Chlorpromazine Hepatotoxicity Manifested by a Selective and Sustained Rise of Serum Alkaline Phosphatase Activity

Report of a Case

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HEPATIC INJURY due to chlorpromazine is a well-recognized clinical and pathologic entity. Typically, the patient presents with fever, malaise, and hepatic chemistry results suggesting obstructive jaundice. Most often, signs of hepatocellular injury are minimal. The present report describes a patient who appears to have had a unique reaction to chlorpromazine marked by a very high and selective increase in serum alkaline phosphatase activity.

CASE REPORT

L. S. (VA 45838), a 41-year-old Negro man, was admitted to the neuropsychiatric service Oct. 8, 1963, complaining of recent dizziness, of "not feeling too well" for several weeks, and of a "blackout spell." His family had noted increasingly seclusive behavior in the 2 months prior to admission. He had consulted his physician 10 days before entering the hospital and was given chlorthiazide (Diuril), dimenhydrinate (Dramamine), and chlordiazepoxide hydrochloride (Librium) for hypertension and nervousness. For several years the patient had consumed a moderate amount of alcohol, but both the family and the patient insisted that he had used none for the 2 weeks prior to admission.

On examination, the patient was confused, disoriented, and hallucinating. The blood pressure was 160/100; pulse, temperature, and respirations were normal. Results of routine physical and neurological examination were within normal limits. There was no jaundice.

Laboratory studies revealed a hemoglobin of 14.9 gm./100 ml., a white blood count of 9750, and a normal differential count. The urine had a specific gravity of 1.012 and the sediment contained no albumin, sugar, casts, or cells.

On the second hospital day, dephenylhydantoin (Dilantin) and phenobarbital were

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TABLE 1. LABORATORY DATA FOR PATIENT WITH LIVER INJURY PROBABLY DUE TO CHLORPROMAZINE TOXICITY

Date	*Bilirubin (mg./100 ml.)*		*Alk. phosphatase (K.A. U.)*	*Cholesterol (mg./100 ml.)*	*SGOT (U.)*	*TP/AG (gm./100 ml.)*	*BSP retention (%)*	*Thymol turbidity (U.)*
	Direct	*Total*						
10/24/63	0.25	1.05	35.2	—	—	—	14	—
10/30/63	0.25	0.55	40.4	—	68	—	—	—
10/31/63	—	—	58.7	—	—	—	—	4.9
11/ 5/63	—	—	162.0	—	200	—	—	—
11/12/63	0.35	1.05	—	—	45	—	—	—
11/21/63	0.35	—	91.6	—	—	—	—	—
11/26/63	—	—	75.3	—	—	—	—	—
12/ 3/63	—	—	55.7	—	—	—	—	—
1/20/64	—	—	12.6	240	—	4.6/9.4	—	—

given. The next day, chlorpromazine, 50 mg. t.i.d., was added; this was increased on the fourth day to 100 mg. q.i.d. Beginning on the sixth hospital day 2 mg. trifluoperazine (Stelazine) t.i.d. was also given.

The patient's mental status improved gradually. However, 18 days after the onset of chlorpromazine therapy, he complained of fever and malaise. His temperature rose from normal to 38.5°C. No jaundice or abdominal tenderness was noted on physical examination. At the onset of this illness the white blood count was 8500, with 9% eosinophils. The alkaline phosphatase was initially 35.2 K.A. U. and, over the next 2 weeks, it rose to a maximal value of 162 K.A. U. Abnormal values persisted over a period of 3 months, during which time the plasma bilirubin level remained within the normal range. Results of other liver function tests are summarized in Table 1.

With the onset of fever, all medications were stopped. There was a gradual defervescence and general clinical improvement over a period of 5 days. Three days after the fever was noted, the patient complained of discomfort in the right upper quadrant; the liver was found to be tender and slightly enlarged. A percutaneous liver biopsy performed on Nov. 16, during the third week in which liver function tests gave abnormal results, revealed a mononuclear and eosinophilic portal infiltrate without apparent parenchymal cell damage or cholestasis. Mild proliferation of the small bile ducts was also evident.

DISCUSSION

Chlorpromazine hepatic hypersensitivity is perhaps the best studied of all drug-induced hepatic injuries. Dickes *et al.*, in a review of a large number of patients given the drug for psychiatric reasons, reported that almost 50% showed some biochemical alteration of liver function.[1] Abnormal changes usually consisted of slight elevations of serum alkaline phosphatase and BSP retention. Seldom did elevations of serum bilirubin or a recognizable clinical syndrome occur.[1, 2]

A clinical reaction with jaundice has been reported in about 2% of patients receiving the drug.[3] Generally, fever, malaise, and jaundice appear approximately 3 weeks after the onset of chlorpromazine administration. Peripheral blood eosinophilia and mild hepatomegaly are common. The reaction is considered by most to be one of a hypersensitivity nature rather than a true toxic reaction.[4]

Histologically, the most common description of chlorpromazine icterus includes centrilobular cholestasis which is often, but not always, accompanied by an early eosinophilic portal tract infiltrate.[3] Liver function tests suggest obstructive jaundice. Alkaline phosphatase and direct-reacting bilirubin levels are usually elevated, and BSP retention occurs.

In his excellent monograph, Zimmerman redefines the pathologic reaction as "hepatocannalicular," implying involvement of both hepatic parenchyma and ductal systems.[3] He reviewed a large number of cases and noted an absence in about 50% of hepatic chemistry results indicating obstruction. One quarter of the patients demonstrated significant

rise in flocculation and turbidity test results, or histologic evidence of hepatocellular necrosis.

Although multiple drug exposures and a history of alcoholism obviously raise the question as to the etiology of the hepatic injury in the patient herein reported, the peripheral blood eosinophilia and subsequent course clearly suggest chlorpromazine as the most likely offender. The illness and findings in the present patient differ from the usual picture in two important aspects: (1) the elevation of alkaline phosphatase to a maximal value of 162 K.A. U. is far out of the range seen in the usual reaction, and (2) this persistent alkaline phosphatase elevation occurred without either serum hyperbilirubinemia or apparent cholestasis in the biopsy specimen in a patient who was clinically ill with fever, malaise, and hepatomegaly as the major symptoms. Modest elevation of alkaline phosphatase activity without hyperbilirubinemia has been noted in several circumstances. This combination most often occurs in Paget's disease, in metastatic carcinoma, and with chronic intermittent biliary obstruction. Werther and Korelitz[4] reported 2 patients, both taking chlorpromazine, in whom the alkaline phosphatase values were elevated to 21 and 32 K.A. U., while the serum bilirubin remained normal. A similar disproportion between serum alkaline phosphatase activity and bilirubin concentration has been reported by Ross *et al.*[5] as characteristic of infiltrative diseases of the liver such as tuberculosis, sarcoidosis, Hodgkin's disease, and amyloidosis.

The mechanism responsible for this unusually high rise in alkaline phosphatase in the absence of hyperbilirubinemia remains obscure.[6] Leak of serum enzymes from an injured cell seems unlikely as the sole explanation, since there was no histologic evidence of cell damage and a very transient rise in SGOT was the only other chemical evidence of cell injury. The sustained elevation of alkaline phosphatase without bilirubin in the urine or some rise of serum bilirubin makes a purely small bile duct obstructive process unlikely. In addition, the usual picture of intrahepatic cholestasis, as recognized by light microscopy, was absent.

The major pathologic findings in this patient were cellular infiltration in the portal areas and mild bile duct proliferation. This picture was noted as the most significant feature of postarsphenamine jaundice by Hanger and Gutman in 1940,[7] and has been noted as a prominent feature in some cases of chlorpromazine jaundice by Popper.[6] Central cholestasis, the more common histologic reaction in patients exposed to chlorpromazine, often occurs without involvement of the portal areas. Since both effects may frequently be seen in varying proportion in the same patient, they may be considered to be two parts of the same reaction.

Recent electron microscopic studies may provide a possible model for

this type of drug reaction. In rats, extrahepatic obstruction and drugs known to produce cholestasis in man produce no bile retention visible by the light microscope. Under the electron microscope, however, dilatation of bile canaliculi and loss of microvilli have been noted.[7] Similar changes have been seen in liver biopsy specimens from patients with the usual light-microscope findings of chlorpromazine liver injury.[10] Kniffen and Schaffner suggest that the definition of cholestasis be extended to include these ultrastructural findings.[9] Though the significance of these observations is not well understood at present, they may indicate a common ultrastructural locus for various forms of obstructive hepatic injury.

SUMMARY

A patient with liver injury, probably due to chlorpromazine toxicity, is presented. Unusual features of this patient's illness included an extremely high and persistent elevation of alkaline phosphatase level without hyperbilirubinemia and lack of centrilobular bile stasis on liver biopsy.

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